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### **Research Article**



## Retrospective Review of 5-Year Experience with Intravesical Injections of Bupivacaine, Triamcinalone and Gentamicin for Interstitial Cystitis/ Bladder Pain Syndrome

Gupta Sandhya\*, Rane Ajay, Vengavati Venkat, Achari Mugundan and Fullerton Alexandra

Waterdale Pkt, Idalia, QLD, Australia

#### \*Corresponding author

Sandhya Gupta, Waterdale Pkt, Idalia, QLD, Australia, Tel: +61-421800784. E-mail: sums.sandhya@gmail.com

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#### ABSTRACT

**Objectives:** Interstitial cystitis (IC) is a poorly diagnosed condition that produces chronic and painful symptoms that affect the sufferer's quality of life. This article reports on the outcomes and trends of patients who received an intravesical cocktail injection of triamcinolone (steroid), gentamycin, and bupivacaine for symptom control in interstitial cystitis over a 5-year period.

**Methods:** A retrospective analysis was performed on 408 patients with Interstitial Cystitis/Bladder Pain Syndrome who were treated with an intravesical cocktail injection (triamcinolone, gentamicin, and bupivacaine) over a 5-year period (Jan 2015 – Dec 2019). All patients had been diagnosed with IC/BPS and had received first-line treatment as per the American Urology Association IC/BPS Guidelines. The age of the patients, the number of treatments, and the duration between each treatment were analysed using Spearman's rho analysis.

**Results:** In our cohort of patients, 264 patients (64.7%) responded well to just one intravesical cocktail therapy, 93 patients (22.7%) required two treatments, and 51 patients (12.5%) required 3 or more treatments for their symptom control. The longest interval between treatment delivery was between the first and second dose, an average of 328.2 days. A trend of sequentially shorter intervals between injections was demonstrated in those patients who required more than one therapeutic injection.

**Conclusions:** The majority of the cohort patients, 87.5%, responded well and found sufficient symptom relief from just one or two intravesical injections. However, patients who required repeated injections received them at progressively shorter intervals, signifying poor efficacy of symptom control in this subset of patients.

**Keywords:** Bladder Pain Syndrome, Interstitial Cystitis, Intravesical Injection, Treatment

#### Introduction

Interstitial cystitis (IC), also known as Bladder Pain Syndrome, is a chronic and often debilitating condition. The syndrome clinically manifests as dysuria, frequency, urgency, nocturia and bladder pain in the absence of infection or other causes. Interstitial cystitis affects five times more women than men [1]. In the United States, the yearly incidence is 2.6 per 10,000 women.

The aetiology of IC/BPS is uncertain, but several theories have been proposed including bladder wall glycosaminoglycan damage, autoimmune, neurogenic and infective aetiologies [2]. Though the therapeutic mechanism is unknown, intravesical injection of various agents such as triamcinolone, dimethyl sulfoxide (DMSO), heparin and lidocaine have been reported to be effective in the treatment of IC/BPS symptoms and are recommended as second line treatment agents in the AUA Guideline of Interstitial Cystitis [3]. Multiple studies demonstrate the moderate efficacy of intravesical injections of DMSO through objective results including an increase in bladder capacity post treatment, and also subjectively through drastic reductions in patient reported Pelvic Pain and Urgency/Frequency (PUF) symptom scales [4,5].

The optimal number of treatments required and intervals between treatment dates have been previously observed in a small cohort by Funaro et al in 2018 [6]. This study demonstrated good efficacy of using submucosal steroid injections for reducing symptoms of IC. Currently, studies assessing the patterns of repeated treatment amongst larger cohort groups are limited.

Recognizing the various proposed aetiologies of IC/BPS, we used a cocktail of a steroid (triamcinolone acetate), a local anaesthetic (bupivacaine) and an antibiotic (gentamicin) for the treatment of our patients.

#### **Materials and Methods**

This is a retrospective review of 408 patients with 647 episodes of intravesical cocktail injections (combination of triamcinolone, gentamicin and bupivacaine) performed over a 5- year period (Jan 2015 – Dec 2019). Local Ethics Committee approval was

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#### for the retrospective review.

The diagnosis of IC/BPS was made by flexible cystoscopy, biopsy as needed, a detailed pelvic dysfunction questionnaire and ruling out other causes for the symptoms. Forty-one (10%) patients had Hunner's lesions on cystoscopy. Pain was recorded on the VAS score prior to start of treatment and monitored throughout the follow-ups. All patients received the first line treatments as per the AUA IC/BPS Guideline. These included advice on lifestyle management changes, acid free diet, NSAIDs and amitriptyline for pain control. Patients with urinary tract infection were treated with a course of appropriate antibiotic. Non-responders were offered a bladder injection as a second line treatment option for symptom control. Hydrodistention or intravesical instillation of DMSO, Heparin or Lidocaine was not offered to any patient.

The bladder injection was done under sedation or light general anaesthetic. This was performed using a specific cystoscopic delivery system (Karl Storz) and needles (Bonee, Coloplast). A 20ml drug cocktail was prepared with 0.5% Marcaine (16 ml), 8mg Triancinalone (2 ml) and 80mg Gentamycin (2 ml). Injections were done supratrigonally into the submucosa raising a bleb with aliquots of 2 to 3 ml per site. Specific areas with severe inflammation were additionally targeted during the procedure.

Patients had a phone consultation 24 hours post-surgery to ensure good recovery. All patients were reviewed between 8 and 12 weeks postoperatively by a trained Urogynaecology nurse using a standardised assessment form for pain (VAS score) and other symptom control satisfaction. All patients were also reviewed annually from then on. Patients with continued pain score of more than 6 were offered re-injections. Hence, the number of treatments can be used as an indirect indicator of the effectiveness of the treatment. The number of treatments needed by each patient and the time interval between these treatments were analysed. The association between age and the number of treatments needed was determined using Spearman's rho analysis through the SPSS statistics software.

#### Results

The mean age of our cohort was 61.2 years, with 110 patients (27%) less than 55 years in age highlighting the increased prevalence of severe IC/ BPS in older patients (Figure 1).



Figure 1: Age Distribution of IC/ BPS

On retrospective review, 264 (64.7%) patients needed only one treatment and reported good control of symptoms, especially pain. Ninety-three patients (22.7%) received two treatments, 32 patients (8%) of the patients needed three treatments and only 19 patients (5%) required more than 3 treatments (Figure 2).



Figure 2: Number of intravesical cocktail injections

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Figure 3: Scatter plot of age by number of treatments received

		5								
		Between 2 <sup>nd</sup> and 1 <sup>st</sup>	Between 3 <sup>rd</sup> and 2 <sup>nd</sup>	Between 4 <sup>th</sup> and 3 <sup>rd</sup>	Between 5 <sup>th</sup> and 4 <sup>th</sup>	Between 6 <sup>th</sup> and 5 <sup>th</sup>	Between 7 <sup>th</sup> and 6 <sup>th</sup>	Between 8 <sup>th</sup> and 7 <sup>th</sup>	Between 9 <sup>th</sup> and 8 <sup>th</sup>	Between 10 <sup>th</sup> and 9 <sup>th</sup>
Ν	Valid	145	51	19	8	4	3	2	2	1
	Missing	271	365	397	408	412	413	414	414	415
Mean		328.2	274.94	254.58	162.13	231	93.67	94	144	77
Median		186	174	168	122.5	245	92	94	144	77
Std. Deviation		313.646	237.423	230.482	102.746	61.822	17.559	15.556	74.953	
Range		1611	870	804	328	140	35	22	106	0
Minimum		0	47	99	66	147	77	83	91	77
Maximum		1611	917	903	394	287	112	105	197	77

Table 1: Intervals between treatments in days

#### Discussion

IC/BPS is a complex and challenging syndrome to diagnose, treat and meet patient expectations. The aetiology is incompletely understood and various theories include an autoimmune process, undetectable infection, neuro-muscular incoordination and mental health issues2. There is no direct causation evidence and various aetiology theories are based on association. For example, the autoimmune theory is based on the association of other autoimmune diseases in some patients, similarity age group and the finding of bladder wall glycosaminoglycan (GAG). The infective theory is based on the finding of recent history of culture positive UTI in 18-36% of patients as well as the fact that the sensitivity of urinary cultures is 50-95% depending on the criteria used. The American Urological Association guideline for treatment of IC/BPS recommends a step-wise approach [7-9]. The first line of treatment includes lifestyle modifications, pelvic floor strengthening exercises and multimodality approach. Increasing complexity and severity of symptoms may need pharmacological treatment, oral as well as intravesical, with more invasive treatments such as electrocautery and mucosal excisions reserved for Hunner's ulcers and refractory IC/BPS.

Recognizing the three most accepted aetiologies of IC/BPS, we used a cocktail of a long acting steroid with a highly effective antibiotic and a long acting local anaesthetic to treat our patients over the last 5 years. All three drugs have an excellent track record of decades of usage and reliable safety profiles in the doses and routes of administration used. The use of submucosal injection of triamcinolone (TA) was first reported by Cox et al in patients of refractory Hunner's lesion sub-type of IC/BPS [10]. Rittenberg and Jiang have also reported good results with the use of TA intravesical injections [11,12].

We achieved excellent symptom control in 87.5% of patients with a single or, at the most, two bladder submucosal injections with our cocktail of TA, gentamicin and bupivacaine. A further 7.8% of patients required a third injection before achieving symptom control. Increasing age was found to have a weak correlation with the number of overall treatments (Spearman's rho co-efficient of 0.216) (Figure 3). Whether this correlation reflects better response to bladder steroid injections with age will need to be assessed in greater detail. None of the patients in our study had any post-operative complications and were discharged the same day. There were no long-term adverse effects of the treatment in our follow-up.

While this initial study result demonstrates the safety and good efficacy of the intravesical submucosal cocktail injection, further studies are required to objectively assess the impact on quality of life. Our study is also limited by the absence of a control group. In conclusion, interstitial cystitis affects women of all age groups and symptoms can be chronic and recurrent. The majority of cohort patients responded well to one or two therapeutic injections. However, those patients who required more than two injections, did so at more frequent and shorter intervals between the treatments. This demonstrated that the efficacy of intravesical injections of triamcinolone, gentamycin and bupivacaine for providing sustained symptom relief was greatest for the first and second injections.

Further studies are required to improve the understanding of ways to increase the long-term effectiveness of intravesical steroid injections for IC pain and aid in optimisation of patient care.

#### Conclusions

The majority of the cohort patients, 87.5%, responded well and found sufficient symptom relief from just one or two intravesical injections. However, patients who required repeated injections received them at progressively shorter intervals, signifying poor efficacy of symptom control in this subset of patients.

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The requirement for more than 2 injections can be used as a prognosticator for the efficacy of this treatment. However, a randomized double controlled blind trial will conclusively prove the benefit of this treatment regimen.

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